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EXAMINER

DI NOLA BARON, LILIANA

ART UNIT

PAPER NUMBER

1615

DATE MAILED: 04/09/2003

18

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.

09/503,852

Applicant(s)

TILLY ET AL.

Examiner

Liliana Di Nola-Baron

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 19 February 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 1-23,27-36 and 46-71 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-23,27-36 and 46-71 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

## Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 12.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

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### **DETAILED ACTION**

1. In view of the Applicant's appeal brief filed on February 19, 2003, PROSECUTION IS HEREBY REOPENED. A new ground of rejection is set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) request reinstatement of the appeal.

If reinstatement of the appeal is requested, such request must be accompanied by a supplemental appeal brief, but no new amendments, affidavits (37 CFR 1.130, 1.131 or 1.132) or other evidence are permitted. See 37 CFR 1.193(b)(2).

### ***Information Disclosure Statement***

2. The information disclosure statement (IDS) submitted on August 20, 2002 has been considered by the examiner.

### ***Claim Rejections - 35 USC § 112***

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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4. Claims 1-23 and 46-71 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention:

The invention is directed to methods of protecting a female reproductive system against an artificial or natural insult comprising administering a composition comprising an agent that antagonizes one or more acid sphingomyelinase (ASMase) gene products.

(2) The state of the prior art

The prior art teaches that oocyte apoptosis caused by the chemotherapeutic drug doxorubicin is blocked by sphingosine-1-phosphate (SPP), an ASMase inhibitor.

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(3) The relative skill of those in the art

The relative skill of those in the art is high, but only in the art of controlling cell apoptosis.

(4) The predictability or unpredictability of the art

The predictability or lack thereof in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results from the claimed invention. The lower the predictability, the higher the direction and guidance that must be provided by Applicant.

(5) The breadth of the claims

The claims are very broad. No correlation is established between the different artificial insults: chemical, radiation and surgical, nor between the various possible causes of natural insult: genetic background, physiological factors, environmental factors..

(6) The amount of direction or guidance presented

The amount of direction and guidance provided by Applicant is limited. There is no evidence in the specification that established correlation between the different artificial insults claimed by Applicant, nor, with respect to claims 22 and 23, between some of the diseases, for which the artificial insults are used as therapy. With respect to claims 62-71, no correlation has been established in the specification between the various possible causes of natural insult, which Applicant claims: genetic background, physiological factors and environmental factors..

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(7) The presence or absence of working examples

The working examples present no data on the effect of the compositions of the invention on the treatment of the various diseases.

(8) The quantity of experimentation necessary

The effect of the methods of the invention on the different artificial insults, for which no correlation has been established, and which are the result of therapies used for unrelated diseases, and on natural insults, which may be caused by unrelated factors, cannot be predicted a priori, but must be determined from the case to case by painstaking experimental study in vivo. When the above factors are weighed together, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to determine a possible protecting effect of the methods claimed in the instant application.

5. Claims 27-36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification does not reasonably provide enablement for "preserving, enhancing or reviving" ovarian function or "preventing or ameliorating" menopausal syndromes. The asserted utilities are not believable on their face.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the

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prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

The instant invention is directed to the treatment of ovarian function or menopausal syndrome, comprising the administration of a composition comprising SPP. The state of the art is what prior art knows about the invention. There is no known art, wherein a certain composition is administered to successfully preserve, enhance or revive a body function or prevent a syndrome before the occurrence of malfunction or disease.

The level of ordinary skill is high, but only in the art of treating an ovarian function or menopausal syndrome. The predictability or lack thereof in the art refers to the ability of one skilled in the art the disclosed or known results from the claimed invention. The lower the predictability, the higher the direction and guidance that must be provided by Applicant. In the instant invention, the predictability is very low and , consequently, a high level of direction and guidance must be provided by the Applicant. However, no such guidance is provided and no correlation is present between the experiments in the specification and the claimed utility. The quantity of experimentation required to use the methods as claimed in the instant invention , based on Applicant's disclosure, would be undue burden because one of ordinary skill in the art would have to perform a significant amount of experiments and clinical trials.

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***Claim Rejections - 35 USC § 103***

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

7. Claims 1-23, 27-36 and 46-71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Perez et al. in view of Spiegel and further in view of Igarashi et al.

The claimed invention refers to methods of protecting female reproductive system, preserving or reviving ovarian function, or ameliorating menopausal syndromes in women, comprising administering a composition comprising sphingosine-1-phosphate (SPP).

Perez et al. indicates that conventional cancer therapies, specifically chemotherapy, kill normal cells and one of the most sensitive noncancerous cell type is the ovarian germ cell, and teaches that apoptosis induced by the chemotherapeutic drug doxorubicin is blocked by sphingosine-1-phosphate (See e.g., p. 1228 and Abstract). Perez et al. teaches that exposure of women to a wide spectrum of agents that damage the ovary generally leads to irreversible sterility (See e.g., p. 1228) and the data from the study provide a strong impetus to manipulate apoptosis caused by chemical drugs in oocytes, in vivo, as a potential means to overcome infertility associated with cancer treatment (See e.g., p. 1231).

Perez et al. does not specify the method and dosage of administration of compositions comprising SPP.



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Spiegel provides methods of retarding apoptosis in degenerative diseases, including neurodegenerative diseases and aging, by administration of sphingosine-1-phosphate and derivatives thereof (See e.g., col. 1, lines 9-17). Spiegel teaches that compositions containing SPP may be administered directly to the cells or parenterally to obtain concentrations of 0.1-100  $\mu\text{M}$ , as well as to the epithelial tissues, such as the rectum and the vagina (See e.g., col. 1, line 46 to col. 2, line 42).

Igarashi et al. discloses a method of inhibiting tumor cell chemoinvasion, comprising contacting the tumor cells with an inhibitory amount of sphingosine-1-phosphate (See e.g., col. 1, line 57 to col. 2, line 48). Igarashi et al. provides methods of inhibiting tumor cell chemoinvasion, comprising administering to a host in need of treatment an inhibitory amount of sphingosine-1-phosphate and teaches that said inhibitory amount can be determined using art-recognized methods, such as dose response curves, or clinical trials, and sphingosine-1-phosphate can be administered orally, parenterally and topically, with suitable doses of sphingosine-1-phosphate depending upon the particular medical application and that the number of doses, daily dosage and course of treatment may vary from individual to individual (See e.g., col. 7, lines 32-65).

Thus, Spiegel and Igarashi et al. provide the teachings that SPP is administered in vivo and disclose a dosage for said administration. Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to apply the teachings of Perez et al. and Spiegel to devise methods of protecting the female reproductive system, reviving the ovarian function or ameliorating menopausal syndromes in women, comprising administering SPP

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compositions, and determining the mode and dosage of administration according to the teachings of Igarashi et al. Because of the teachings of Spiegel, that sphingosine-1-phosphate is effective in treating aging diseases, and the teachings of Igarashi et al., that sphingosine-1-phosphate inhibits tumor cell chemoinvasion, one of ordinary skill in the art would have a reasonable expectation that the methods claimed in the instant application would be successful. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

#### ***Response to Arguments***

8. Applicant's arguments filed on February 19, 2003 have been fully considered but they are not persuasive.

9. Applicant argues that Perez et al. discloses studies, which were performed in vitro and contains specific statements of doubt as to whether the results obtained in vitro can be extrapolated to in vivo treatment of the female reproductive system, and Spiegel and Igarashi et al. are not directed to the field of Applicant's invention. In response to said arguments, it is noted that the statement in Perez et al. to which Applicant refers (p. 1230) does not imply that SPP cannot be effective in vivo, but rather contemplates the factors required for preserving fertility in vivo. Peretz et al. provides the general teachings that SPP is effective in treating apoptosis in oocytes previously treated with a chemotherapeutical drug and the motivation to look for similar results in vivo, as a potential means to overcome infertility associated with cancer treatment (See e.g., p. 1231). The examiner relies on Spiegel and Igarashi et al. for their teachings that SPP is administered in vivo and the disclosure of a dosage for said administration. With respect to the

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field of Applicant's invention, Spiegel teaches the use of sphingosine-1-phosphate (SPP) to retard apoptosis in degenerative diseases, including aging, which is defined by Applicant as a natural insult (See Applicant's specification, p. 15). Additionally, Spiegel teaches that SPP may be administered to the epithelial tissues, such as the rectum and the vagina (See e.g., Col. 1, line 46 to col. 2, line 26). Igarashi et al. provides the teachings that sphingosine-1-phosphate can be administered orally, parenterally and topically (See e.g., col. 7, lines 32-65). Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to combine the teachings of Perez et al., Spiegel and Igarashi et al. to devise methods of protecting the female reproductive system, reviving the ovarian function or ameliorating menopausal syndromes in women, comprising administering SPP compositions, and determining the mode and dosage of administration according to the teachings of the prior art. The expected result would have been a successful method of protecting a female reproductive system against natural or artificial insults.

10. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Perez et al. contemplates methods of treatment of the female reproductive system using sphingosine-1-phosphate in vivo based on studies, which were performed in vitro, Spiegel teaches the use of sphingosine-1-phosphate (SPP) to retard apoptosis in degenerative diseases,

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including aging, and Igarashi et al. provides methods comprising administering to a host in need of treatment an inhibitory amount of sphingosine-1-phosphate. Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to combine the teachings of Perez et al., Spiegel and Igarashi et al. to device methods of protecting the female reproductive system, reviving the ovarian function or ameliorating menopausal syndromes in women, comprising administering SPP compositions, and determining the mode and dosage of administration according to the teachings of the prior art. The expected result would have been a successful method of protecting a female reproductive system against natural or artificial insults.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Liliana Di Nola-Baron whose telephone number is 703-308-8318. The examiner can normally be reached on Monday through Thursday, 5:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on 703-308-2927. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3592 for regular communications and 703-305-3592 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 308-1234/ 1235.



April 7, 2003



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